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- (54) **Antibronchospastic
water-soluble pharmaceutical
compositions**
- (57) Antibronchospastic water-soluble compositions comprise the compounds formed from theophylline and amino acids, e.g. lysin or arginine.

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SPECIFICATION

Antibronchospastic water-soluble pharmaceutical compositions.

5 The present invention relates to antibronchospastic water-soluble theophylline salts with basic amino acids. More particularly the invention pertains to pharmaceutical compositions consisting of 10 theophylline water-soluble salts with lysine and arginine and to a process for preparing the same.

It is well known from the prior art pertaining to bronchodilator pharmaceutical preparations that the theophylline (1,3-dimethylxanthine) is a natural substance characterised by significant antibronchospastic properties to be ascribed to the inhibition of the phosphodiesterase and to the increase of the intracellular AMPC.

However, it is likewise known that the low water-solubility of theophylline does not allow the preparation of solutions having therapeutically significant concentrations so as to confine its use to preparations in the form of capsules, tablets and suppositories.

25 The procedures usually adopted at the present time to obtain a therapeutically acceptable water-solubility are based on the salification of the theophylline by means of organic bases such as ethylenediamine, choline, glucamine, and the products obtained thereby are well known and have long been used in therapeutic practice.

However it is to be pointed out that it has resulted from the clinical use, these products are not free from toxicity phenomena and in many cases do not 35 have an acceptable tolerance.

Therefore it will be easily understood the increasing demand for a theophylline composition in which the necessary water-solubility is associated to a minor toxicity and an improved tolerance.

40 It appears that this problem may be satisfactorily solved according to the present invention of preparing theophylline salts with basic amino acids, preferably lysine or arginine, which are pharmaceutically acceptable for producing pharmaceutical preparations having a theophyllinic activity.

The suggestion of utilising the lyophilised form is of great importance to allow the use of the composition in an aqueous solution, assuring an improved stability of the active constituent.

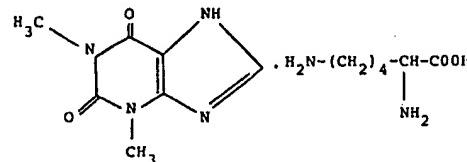
50 Accordingly it is the main object of this invention to provide an antibronchospastic, water-soluble composition consisting of theophylline salts with a basic amino acid. In the preferred embodiment, as aforesaid, lysine or arginine is used as the basic amino acid.

55 The present invention will be now described in the following Examples with particular reference to some preferred embodiments.

Example 1.

60 *Lysine Theophyllinate*

Empirical formula : C₁₃H₂₂N₆O₄ Structural formula:



Molecular weight : 326.36

N contents : 25.76%

Composition : Theophylline 55.21%, Lysine

65 44.79%

Preparation process.

180.17g (1 mole) of theophylline and 219.20g (1.5 moles) of lysine are hot-dissolved in 400ml of H₂O.

The solution is concentrated under vacuum until 70 dryness, the bath temperature being kept lower than 50°C.

The residue is crystallised from 4.5 l of 96% ethyl alcohol. The precipitate, obtained by cooling the solution under stirring, is filtered.

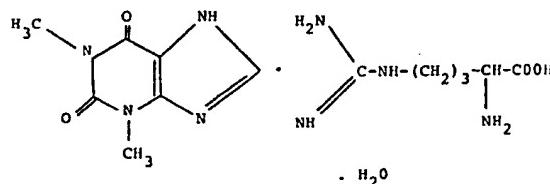
75 260 g: Yield 80% mp:195-205°C (decomposition)

Example II

Arginine Theophyllinate.

Empirical formula : C₁₃H₂₂N₈O₄.H₂O

80 Structural formula:



Molecular weight : 372/38

N Contents : 30.09%

Composition : Theophylline 48.38%, Arginine 46.78%H₂O 4.84%.

85 *Preparation process.*

180.17 g (1 mole) of theophylline and 174.20 g (1 mole) of arginine are hot-dissolved in 800 ml of H₂O.

The cooling of the solution forms a crystalline precipitate (320 g) having a melting point of 200-205°C 90 (decomposition). Yield 86%.

The identity and purity of the salts can be determined by the following analytical operations:

- (a) nitrogen test according to the Dumas method
- (b) titration of amine nitrogen by the poten-

95 tiometric method in anhydrous environment (solvent: glacial acetic acid) by means of HC₁₀, 0.1N in glacial acetic acid.

(c) UV spectrophotometric titration in HC₁ 0.1N.

The pharmaceutical activity has been preliminarily

100 checked by the determination of:

LD₅₀ per os in the mouse

Lysine theophyllinate 1.12 m Mole/kg

Arginine theophyllinate 1.75 m Mole/kg

Antibronchospastic activity in awake guinea-pigs

105 according to the modified Armitage's method (Brit.

J. Pharmacol. 16, 59; 1961); the activity is expressed as an index with respect to the theophylline made equal to 1.

Lysine theophyllinate 1.08

110 Arginine theophyllinate 0.8

